Amendments to the Specification:

Please replace the paragraph beginning at page 2, line 32, with the following rewritten paragraph:

RNase HI from E.coli is the best-characterized member of the RNase H family. The 3-dimensional structure of E.coli RNase HI has been determined by x-ray crystallography, and the key amino acids involved in binding and catalysis have been identified by site-directed mutagenesis (Nakamura et al., *Proc. Natl. Acad. Sci. USA*, 1991, 88, 11535-11539; Katayanagi et al., *Nature*, 1990, 347, 306-309; Yang et al., Science, 1990, 249, 1398-1405; Kanaya et al., *J. Biol. Chem.*, 1991, 266, 11621-11627). The enzyme has two distinct structural domains. The major domain consists ~~of four á helices~~ of four α helices and ~~one large á sheet~~ one large β sheet composed of three ~~antiparallel á strands~~ antiparallel β strands. The Mg^{2+} binding site is located ~~on the á sheet~~ on the β sheet and consists of three amino acids, Asp-10, Glu-48, and Gly-11 (Katayanagi et al., *Proteins: Struct., Funct., Genet.*, 1993, 17, 337-346). This structural motif of the Mg^{2+} binding site surrounded ~~by á strands~~ by β strands is similar to that ~~in DNase I~~ in DNase I (Suck, D., and Oefner, C., *Nature*, 1986, 321, 620-625). The minor domain is believed to constitute the

predominant binding region of the enzyme and is composed of ~~an α helix~~ an α helix terminating with a loop. The loop region is composed of a cluster of positively charged amino acids that are believed to bind electrostatistically to the minor groove of the DNA/RNA heteroduplex substrate. Although the conformation of the RNA/DNA substrate can vary from A-form to B-form depending on the sequence composition, in general RNA/DNA heteroduplexes adopt an A-like geometry (Pardi et al., *Biochemistry*, 1981, 20, 3986-3996; Hall, K. B., and Mclaughlin, L. W., *Biochemistry*, 1991, 30, 10606-10613; Lane et al., *Eur. J. Biochem.*, 1993, 215, 297-306). The entire binding interaction appears to comprise a single helical turn of the substrate duplex. Recently the binding characteristics, substrate requirements, cleavage products and effects of various chemical modifications of the substrates on the kinetic characteristics of E.coli RNase HI have been studied in more detail (Crooke, S.T. et al., *Biochem. J.*, 1995, 312, 599-608; Lima, W.F. and Crooke, S.T., *Biochemistry*, 1997, 36, 390-398; Lima, W.F. et al., *J. Biol. Chem.*, 1997, 272, 18191-18199; Tidd, D.M. and Worenius, H.M., *Br. J. Cancer*, 1989, 60, 343; Tidd, D.M. et al., *Anti-Cancer Drug Des.*, 1988, 3, 117.

Please replace the paragraph beginning at page 15, line 23, with the following rewritten paragraph:

As is known in the art, a nucleoside is a base-sugar combination. The base portion of the nucleoside is normally a heterocyclic base. The two most common classes of such heterocyclic bases are the purines and the pyrimidines. Nucleotides are nucleosides that further include a phosphate group covalently linked to the sugar portion of the nucleoside. For those nucleosides that include a pentofuranosyl sugar, the phosphate group can be linked to ~~either the 2=, 3= or 5= hydroxyl moiety~~ either the 2', 3' or 5' hydroxyl moiety of the sugar. In forming oligonucleotides, the phosphate groups covalently link adjacent nucleosides to one another to form a linear polymeric compound. In turn the respective ends of this linear polymeric structure can be further joined to form a circular structure, however, open linear structures are generally preferred. Within the oligonucleotide structure, the phosphate groups are commonly referred to as forming the internucleoside backbone of the oligonucleotide. The normal linkage or backbone of RNA and DNA ~~is a 3= to 5= phosphodiester~~ is a 3' to 5' phosphodiester linkage.

Please replace the paragraph beginning at page 16, line 18, with the following rewritten paragraph:

Preferred modified oligonucleotide backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates ~~including 3'-alkylene~~ including 3'-alkylene phosphonates, 5'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates ~~including 3'-amino~~ including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, selenophosphates and boranophosphates having ~~normal 3'-5' linkages, 2'-5' linked analogs~~ normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein one or more internucleotide linkages is a 3' to 3', 5' to 5' or 2' to 2' linkage. Preferred oligonucleotides having inverted polarity comprise a single 3' to 3' linkage at the 3'-most internucleotide linkage i.e. a single inverted nucleoside residue which may be abasic (the nucleobase is missing or has a hydroxyl group in place thereof). Various salts, mixed salts and free acid forms are also included.

Please replace the paragraph beginning at page 19, line 3, with the following rewritten paragraph:

Modified oligonucleotides may also contain one or more substituted sugar moieties. Preferred oligonucleotides comprise one of the following at the 2' position: OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Particularly preferred are $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nOCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, and $O(CH_2)_nON[(CH_2)_nCH_3)]_2$, where n and m are from 1 to about 10. Other preferred oligonucleotides comprise one of the following ~~at the 2- position:~~ at the 2' position: C_1 to C_{10} lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, poly-alkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. A preferred modification includes 2'-methoxyethoxy (2'-O-$CH_2CH_2OCH_3$, also known as 2'-O-(2-

methoxyethyl) or 2'-MOE) (Martir et al., *Helv. Chim. Acta*, 1995, 78, 486-504) i.e., an alkoxyalkoxy group. A further preferred modification ~~includes 2= dimethylaminooxyethoxy~~ includes 2'-dimethylaminooxyethoxy, i.e., a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2'-DMAOE, as described in examples hereinbelow, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), i.e., 2'-O-CH_2-O-CH_2-$N(CH_3)_2$, also described in examples hereinbelow.

Please replace the paragraph beginning at page 20, line 6, with the following rewritten paragraph:

Other preferred modifications include 2'-methoxy (2'-O-CH_3), 2'-aminopropoxy (2'-$OCH_2CH_2CH_2NH_2$), 2'-allyl (2'-CH_2-CH=CH_2), 2'-O-allyl (2'-O-CH_2-CH=CH_2) and 2'-fluoro (2'-F). The 2'-modification may be in the arabino (up) position or ribo (down) position. A preferred 2'-arabino modification is 2'-F. Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide ~~or in 2= 5= linked~~ or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative

United States patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S.: 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; 5,792,747; and 5,700,920, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference in its entirety.

Please replace the paragraph beginning at page 32, line 9, with the following rewritten paragraph:

An internet search of the XREF database in the National Center of Biotechnology Information (NCBI) yielded 2 overlapping human expressed sequence tags (ESTs), GenBank accession numbers W05602 and H43540, homologous to yeast RNase H11 (RNH2) protein sequence (GenBank accession number Z71348; SEQ ID NO: 4 shown in Figure 1), and its *C. elegans* homologue (accession number Z66524, of which amino acids 396-702 of gene TT3H5.2 correspond to SEQ ID NO: 3 shown in Figure 1). Three sets of oligonucleotide primers hybridizable to one or both of the human RNase HII EST sequences were synthesized. The sense primers were AGCAGGCGCCCCTTCGACGC (H1A; SEQ ID NO: 13),

CCCGCTCCTGCAGTATTAGTTCTTGC (H1B; SEQ ID NO: 14) and TTGCAGCTGGTGGTGGCGGCTGAGG (H1C; SEQ ID NO: 15). The antisense primers were TCCAATAGGGTCTTTGAGTCTGCCAC (H1D; SEQ ID NO: 16), CACTTTCACCGCCTCCAGATCTGCC (H1E; SEQ ID NO: 17) and CCGAGCCAGGGGACAATAACAGATGG (H1F; SEQ ID NO: 18). The human RNase HII 3' cDNA derived from the EST sequence were amplified by polymerase chain reaction (PCR), using human liver Marathon ready cDNA (Clontech, Palo Alto, CA) as templates and H1A or H1B/AP1 (for first run PCR) as well as H1B or H1C/AP2 (for second run PCR) as primers. AP1 and AP2 are primers designed to hybridize to the Marathon ready cDNA linkers (linking cDNA insert to vector). The fragments were subjected to agarose gel electrophoresis and transferred to nitrocellulose membrane (Bio-Rad, Herculos CA) for confirmation by Southern blot, using a ^{32}P-labeled H1E probe (for 3' RACE). The confirmed fragments were excised from the agarose gel and purified by gel extraction (Qiagen, Germany), then subcloned into a zero-blunt vector (Invitrogen, Carlsbad, CA) and subjected to DNA sequencing. The human ~~RNase HII 5= cDNA~~ RNase HII 5' cDNA from the EST sequence was similarly amplified ~~by 5= RACE~~ by 5' RACE. The overlapping sequences were aligned and combined by the assembling programs of MacDNASIS v. 3.0 (Hitachi Software Engineering Co., America, Ltd.). The full

length human RNase HII open reading frame nucleotide sequence obtained is provided herein as SEQ ID NO: 12. Protein structure and analysis were performed by the program MacVector v6.0 (Oxford Molecular Group, UK). The 299-amino acid human RNase HII protein sequence encoded by the open reading frame is provided herein as SEQ ID NO: 1.

Please replace the paragraph beginning at page 33, line 18, with the following rewritten paragraph:

(Stratagene, La Jolla, CA) was screened using ~~the 3'-RACE~~ the 3' RACE products as specific probes. The positive cDNA clones were excised into pBluescript phagemid from lambda phage and subjected to DNA sequencing. Sequencing of the positive clones was performed with an automatic DNA sequencer by Retrogen Inc. (San Diego, CA).

Please replace the paragraph beginning at page 33, line 25, with the following rewritten paragraph:

Total RNA was isolated from different human cell lines (ATCC, Rockville, MD) using the guanidine isothiocyanate method (21). ~~Ten ig of~~ Ten ug of total RNA was separated on a 1.2 % agarose/formaldehyde gel and transferred to Hybond-N+ (Amersham,

Arlington Heights, IL) followed by fixing using UV crosslinker (Strategene, La Jolla, CA). The premade multiple tissue Northern Blot membranes were also purchased from Clontech (Palo Alto, CA). To detect RNase HII mRNA, hybridization was performed by using ^{32}P-labeled human RNase H II cDNA in Quik-Hyb buffer (Strategene, La Jolla, CA) ~~at 60 EC~~ at 68°C for 2 hours. After hybridization, membranes were washed in a final stringency of 0.1XSSC/0.1%SDS ~~at 60 EC~~ at 60°C for 30 minutes and subjected to auto-radiography.

Please replace the paragraph beginning at page 34, line 18, with the following rewritten paragraph:

The cDNA fragment encoding the full RNase HII protein sequence was amplified by PCR using 2 primers, one of which contains a restriction enzyme NdeI site adapter and six histidine (his-tag) codons and a 22-base pair protein N terminal coding sequence, the other contains an XhoI site and 24 bp protern C-terminal coding sequence including stop codon. The fragment was cloned into expression vector pET17b (Novagen, Madison, WI) and confirmed by DNA sequencing. The plasmid was transfected into E.coli BL21(DE3) (Novagen, Madison, WI). The bacteria were grown in LB medium ~~at 37EC~~ at 37°C and harvested when the OD_{600} of the culture ceached 0.8, in accordance with procedures described by

Ausubel et al., (Current Protocols in Molecular Biology, Wiley and Sons, New York, NY, 1988). Cells were lysed in 8M urea solution and recombinant proteir was partially purified with Ni-NTA agarose (Qiagen, Germany). Further purification was performed with C4 reverse phase chromatography (Beckman, System Gold, Fullerton, CA) with 0.1% TFA water and 0.1% TFA acetonitrile gradient of 0% to 80% in 40 minutes as described by Deutscher, M. P., (Guide to Protein Purification, Methods in Enzymology 182, Academic Press, New York, NY, 1990). The recombinant proteins and control samples were collected, lyophilized and subjected to 12% SDS-PAGE as described by Ausubel et al. (1988) (Current Protocols in Molecular Biology, Wiley and Sons, New York, NY). The purified protein and control samples were resuspended in 6 M urea solution containing 20 mM Tris HCl, pH 7.4, 400 mM NaCl, 20% glycerol, 0.2 mM PMSF, 40 mM DTT, ~~10 ig/ml aprotinin~~ 10 ug/ml aprotinin and leupeptin, and refolded by dialysis with decreasing urea concentration from 6 M to 0.5 M as well as DTT concentration from 40 mM to 0.5 mM as described by Deutscher, M. P., (Guide to Protein Purification, Methods in Enzymology 182, Academic Press, New York, NY, 1990). The refolded proteins were concentrated (10 fold) by Centricon

(Amicon, Danvers, MA) and subjected to an RNase H activity assay as described in subsequent examples.

Please replace the paragraph beginning at page 35, line 23, with the following rewritten paragraph:

A ^{32}P-end-labeled 17-mer RNA, GGGCGCCGTCGGTGTGG (SEQ ID NO: 19) described by Lima, W. F. and Crooke, S. T. (*Biochemistry*, 1997 36, 390-398), was gel-purified as described by Ausubel et al. (*Current Protocols in Molecular Biology*, Wiley and Sons, New York, NY, 1988) and annealed with a tenfold excess of its complementary 17-mer oligodeoxynucleotide. Annealing was done in 10 mM Tris HCl, pH 8.0, 10 mM MgCl, 50 mM KCl and 0.1 mM DTT to form one of two different substrates: single strand (ss) RNA probe and full double strand (ds) RNA/DNA duplex. Each of these substrates was incubated with RNase HII protein samples (isolated as described in the previous example), or with the previously-cloned human RNase HI (Wu et al., 1999, J. Biol. Chem. 274, 28270-28278) ~~at 37EC~~ at 37°C for 5 minutes to 60 minutes at the same conditions used in the annealing procedure and the reactions were terminated by adding EDTA in accordance with procedures described by Lima, W. F. and Crooke, S. T. (*Biochemistry*, 1997,

36, 390-398). The reaction mixtures were precipitated with TCA centrifugation and the supernatant was measured by liquid scintillation counting (Beckman LS6000IC, Fullerton, CA). An aliquot of the reaction mixture was also subjected to denaturing (8 M urea) acrylamide gel electrophoresis in accordance with procedures described by Lima, W. F. and Crooke, S. T. (*Biochemistry*, 1997, 36, 390-398) and Ausubel et al. (*Current Protocols in Molecular Biology*, Wiley and Sons, New York, NY, 1988). The gels were then analyzed and quantified using a Molecular Dynamics PhosphorImager. After 60 minutes, cleavage of the substrate RNA/DNA duplex was detectable.